

We claim:

1. A composition for disruption of a membrane comprising a conjugate comprising a membrane disruptive component comprising a polymer which is hydrophobic under the conditions where the membrane is to be disrupted, and a hydrophilic component selected from the group consisting of a hydrophilic agent to be delivered, hydrophilic groups linkable or linked to the hydrophobic polymer in an amount effective to make the conjugate hydrophilic, and a hydrophilic polymer linkable to the hydrophobic polymer effective to make the conjugate hydrophilic, wherein the hydrophilic component is coupled to the membrane disruptive component via a linkage which is cleaved as a function of pH.
2. The composition of claim 1 wherein the hydrophilic component is selected from the group consisting of hydrophilic groups or a hydrophilic polymer, further comprising a therapeutic, diagnostic or prophylactic agent to be delivered to a cell or cell organelle.
3. The composition of claim 2 wherein the agent is selected from the group consisting of proteins, peptides, nucleotide molecules, saccharides, polysaccharides, small organic molecules, and combinations thereof.
4. The composition of claim 1 wherein the hydrophobic polymer is selected from the group consisting of synthetic vinyl-type hydrophobic polymers and their hydrophilic derivatives that become hydrophobic at the pH of the endosome, non-vinyl or naturally-derived polymers and their hydrophilic derivatives that become hydrophobic at the pH of the endosome, membrane disruptive peptides, phospholipid bilayer disrupting agents, and polymers which become membrane disruptive upon exposure to a stimulus other than pH.
5. The composition of claim 1 wherein the hydrophilic groups are coupled directly to the hydrophobic polymer.
6. The composition of claim 1 wherein the hydrophilic groups are selected from the group consisting of hydroxyacids, amines, thiols, carboxyl group, amino acids, and small molecules including these groups.

7. The composition of claim 1 comprising a hydrophobic polymer linked to hydrophilic groups wherein the hydrophilic groups are protonated at the site where the membrane is to be disrupted to form a hydrophobic polymeric membrane disruptive component.
8. The composition of claim 1 wherein the linkages coupling the hydrophilic component to the membrane disruptive component are selected from the group consisting of acetals, orthoesters, cis-aconityl groups, carboxylic acid hydrazones, phosphamides, esters, Schiff bases, vinyl ethers, dithioacetals, tert butyl esters, and carbamates, urethanes, anhydrides, polysaccharides, amides, esters, ethers, thioureas, ureas, thioesters, sulfenamides, phosphoroamidates, and amine N-oxides.
9. The composition of claim 2 wherein the agent to be delivered is coupled to either the hydrophilic or membrane disruptive component by a degradable or disruptable linkage.
10. The composition of claim 9 wherein the linkage is degradable upon exposure to a change in pH.
11. The composition of claim 10 wherein the linkage is selected from the group consisting of acetals, orthoesters, cis-aconityl groups, carboxylic acid hydrazones, phosphamides, esters, Schiff bases, vinyl ethers, dithioacetals, tert butyl esters, and carbamates, urethanes, anhydrides, polysaccharides, amides, esters, ethers, thioureas, ureas, thioesters, sulfenamides, phosphoroamidates, and amine N-oxides.
12. The composition of claim 8 wherein the linkage is disruptable upon exposure to a physical or chemical stimulus.
13. The composition of claim 1 wherein the conjugate further comprises a ligand specifically binding to a target molecule.
14. The composition of claim 2 wherein the agent to be delivered is complexed to a polymeric component of the conjugate.
15. The composition of claim 1 wherein the hydrophilic component is linked to the membrane disruptive agent by a pH sensitive linkage, wherein the pH sensitive linkage is stable at a pH between 6.8 and 8 and disrupted at a pH less

than pH 6.5, and the linkage will hydrolyze within about 30 to 60 minutes at a pH between 5.0 and 5.5.

16. The composition of claim 1 further comprising a pharmaceutically acceptable carrier for delivery of the conjugate to a cell or organelle.

17. The composition of claim 16 wherein the carrier is selected from the group consisting of carriers for systemic, local, or topical delivery of the conjugate.

18. The composition of claim 1 further comprising a composition enhancing membrane penetration.

19. The composition of claim 2 wherein the agent to be delivered is a nucleotide molecule selected from the group consisting of antisense, ribozymes, ribozyme guide sequences, triplex forming oligonucleotides, and genes.

20. A method of making a composition for disruption of a membrane comprising forming a conjugate comprising

a membrane disruptive component comprising a polymer which is hydrophobic under the conditions where the membrane is to be disrupted, and a hydrophilic component selected from the group consisting of a hydrophilic agent to be delivered, hydrophilic groups linkable to the hydrophobic polymer in an amount effective to make the conjugate hydrophilic, and a hydrophilic polymer linkable to the hydrophobic polymer effective to make the conjugate hydrophilic,

wherein the hydrophilic component is coupled to the membrane disruptive component via a linkage which is cleaved as a function of pH.

21. The method of claim 20 wherein the hydrophilic component is selected from the group consisting of hydrophilic groups or a hydrophilic polymer, further comprising linking to the conjugate a therapeutic, diagnostic or prophylactic agent to be delivered to a cell or cell organelle.

22. The method of claim 20 wherein the hydrophilic groups are coupled directly to the hydrophobic polymer.

23. The method of claim 20 wherein the hydrophilic component is linked to the membrane disruptive component by a linkage selected from the group

consisting of acetals, orthoesters, cis-aconityl groups, carboxylic acid hydrazones, phosphamides, esters, Schiff bases, vinyl ethers, dithioacetals, tert butyl esters, and carbamates, urethanes, anhydrides, polysaccharides, amides, esters, ethers, thioureas, ureas, thioesters, sulfenamides, phosphoramidates, and amine N-oxides.

24. The method of claim 21 wherein the agent to be delivered is coupled to either the hydrophilic or membrane disruptive component by a degradable or disruptable linkage.

25. The method of ~~claim 20~~ wherein the conjugate further comprises a ligand specifically binding to a target molecule.

26. The method of ~~claim 21~~ wherein the agent to be delivered is complexed to a polymeric component of the conjugate.

27. A method for disrupting a cell or organelle membrane comprising delivering to the cell or organelle a conjugate as defined by any of claims 1-19.

28. The method of claim 27 wherein the cell is a cell in a patient.

29. The method of claim 27 wherein the cell is an endosome in a cell.

30. The method of claim 27 wherein the cell is a bacterial cell.

31. The method of claim 27 wherein the conjugate is used to deliver a therapeutic, prophylactic or diagnostic agent.

32. The method of claim 27 wherein the conjugate is used to make a cell, cell organelle, or microorganism permeable to an analyte, cell or organelle component, drug, or infective agent which is to be analyzed.